REMARKS

These remarks are in response to the Office Action mailed August 12, 2003. Claim 9 has been amended in one aspect to correct typographical errors. Support for the Amendment to claim 9 directed to computer-assisted method for determining a three-dimensional structure of a target amino acid by producing from an alignment a three dimensional reduced protein model comprising representations of side chains of amino acid residues comprising a target protein, wherein said representations of side chains of amino acid residues are converted to interaction centers, and each interaction center comprises a pseudoatom representing a center of mass of the side chain of the represented amino acid to which the interaction center corresponds, and each interaction center is connected to an immediately proximal interaction center and an immediately distal interaction center via a virtual covalent bond to produce an interaction center chain, and then secondary constraints and/or tertiary constraints are applied to a subset of, or all of, the interaction centers of the interaction center chain so as to produce a data set representing a three-dimensional model structure of the target protein can be found, inter alia, on page 10, lines 6 to 32 and on page 31, lines 7 to 18. No new matter is believed to have been introduced.

I. OBJECTION TO THE SPECIFICATION

The specification has been amended. Accordingly, the objection may be withdrawn.

II. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 9-11 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 has been amended to corrected the typographical errors identified by the Examiner. Applicants respectfully request withdrawal of the §112, second paragraph.

III. REJECTION UNDER 35 U.S.C. §102(a)

Claims 9-11 stand rejected under 35 U.S.C. §102(a) as allegedly anticipated by Kolinski et al. (Proceedings of HRCL Workshop on Monte Carlo Approach to Biopolymers and Protein Folding. (1998) P. Grassberge et al., Eds. World Scientific, Singapore/London, pages 100-130). Applicants respectfully traverse this rejection.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

Applicants respectfully aver that Kolinski, HRCL Workshop does not describe a computer-assisted method for determining a three-dimensional structure of a target amino acid sequence by aligning a target amino acid sequence with a template amino acid sequence and producing from the alignment a three dimensional reduced protein model comprising representations of side chains of amino acid residues comprising a target protein, wherein said representations of side chains of amino acid residues are converted to interaction centers and each interaction center comprises a pseudoatom representing a center of mass of the side chain of the represented amino acid to which the interaction center corresponds, and each interaction center is connected to an immediately proximal interaction center and an immediately distal interaction center via a virtual covalent bond to produce an interaction center chain, which is projected onto an underlying cubic lattice to produce a projected chain of interaction centers, and then secondary constraints and/or tertiary constraints are applied to a subset of, or all of, the interaction centers of the interaction center chain to generate a force field comprising short-range interactions, thereby producing a data set representing a three-dimensional model structure of the target protein.

The computer implemented methods of the instant invention use a force field designed entirely of a "knowledge-based" origin. It is noted that some terms, such as the generic short- and long-range potentials, provide a bias toward protein-like short- and long-range correlations (see page 41, lines 29 to 31 of the specification). It is noted that the force used in the methods of the invention approximately reproduce the main features of globular proteins, and does so in a

different geometrical context, namely, using pseudoatoms representing side chain centers of mass. Moreover, the instant invention is based on a less complex representation and simpler definition of the force field, and is more computationally efficient than C-alpha-based models, such as MONSSTER (see page 43, lines 1 to 11, of the specification).

Kolinski, HRCL Workshop does not produce an interaction center chain and project the interaction center chain onto an underlying cubic lattice to produce a projected chain of interaction centers by using a calculated force field comprising short-range interactions as set forth in the specification, as discussed above. Accordingly, because Kolinski, HRCL Workshop is not a single prior source that contains each and every limitation of the claimed invention this rejection 35 U.S.C. 102(a) can be withdrawn.

The Patent Office also alleges that Kolinski, J. Phys. Chem. anticipates Applicants' claims 9-11. Applicants respectfully traverse this rejection.

The Patent Office alleges that Kolinski, J. Phys. Chem. teaches the idea of side chain representation into computer modeling techniques for protein structure, and that the lattice chains of centers of mass of side chains is employed which utilizes Monte Carlo simulation to represent the three-dimensional structure of a target polypeptide.

Applicants respectfully aver that Kolinski, J. Phys. Chem. does not describe a computer-assisted method for determining a three-dimensional structure of a target amino acid sequence by aligning a target amino acid sequence with a template amino acid sequence and producing from the alignment a three dimensional reduced protein model comprising representations of side chains of amino acid residues comprising a target protein, wherein said representations of side chains of amino acid residues are converted to interaction centers and each interaction center comprises a pseudoatom representing a center of mass of the side chain of the represented amino acid to which the interaction center corresponds, and each interaction center is connected to an immediately proximal interaction center and an immediately distal interaction center via a virtual covalent bond to produce an interaction center chain, which is projected onto an underlying cubic lattice to produce a projected chain of interaction centers, and then secondary constraints and/or tertiary constraints are applied to a subset of, or all of, the interaction centers of the

interaction center chain to generate a force field comprising short-range interactions, thereby producing a data set representing a three-dimensional model structure of the target protein.

In contrast, the Kolinski, J. Phys. Chem. model "employs a single united atom representation of amino acid residues. These atoms are centered on protein side groups. Characteristic short-range distance correlations have been built into the model, thereby providing a rather accurate description of protein-like conformational stiffness. *Sequence-specific* interaction schemes have been derived from *sequence similarity* and *sequence-structure* compatibility studies" [emphasis added] (see abstract). The Kolinski, J. Phys. Chem. model "employ[s] only the homology ... of small fragments of *protein sequences*, thereby allowing for the construction of a potential for sequences having no globally homologous counterparts in the structural database." [emphasis added] (see page 4628, right-hand column, last sentence first full paragraph); and, "[t]he purpose of this work is to analyze the role of the generic protein-like regularities seen in protein chains, the role of sequence-specific short-range correlations of the side chain positions, and this interplay." (see the sentence spanning pages 4628 and 4629).

Kolinski, J. Phys. Chem. does not produce an interaction center chain and project the interaction center chain onto an underlying cubic lattice to produce a projected chain of interaction centers by using a calculated force field comprising short-range interactions. Accordingly, because Kolinski, J. Phys. Chem. is not a single prior source that contains each and every limitation of the claimed invention this rejection 35 U.S.C. 102(a) can be withdrawn.

Claims 9-11 are further rejected under 35 U.S.C. §102(a) as allegedly anticipated by Ortiz et al. (Proc. Of the 3rd Pacific Symposium on Biocomputing (1998), Altman et al., Eds., World Scientific Singapore/London, pages 377-388). Applicants respectfully traverse this rejection.

Applicants respectfully aver that Oritz does not describe a computer-assisted method for determining a three-dimensional structure of a target amino acid sequence by aligning a target amino acid sequence with a template amino acid sequence and producing from the alignment a three dimensional reduced protein model comprising representations of side chains of amino acid residues comprising a target protein, wherein said representations of side chains of amino acid

residues are converted to interaction centers and each interaction center comprises a pseudoatom representing a center of mass of the side chain of the represented amino acid to which the interaction center corresponds, and each interaction center is connected to an immediately proximal interaction center and an immediately distal interaction center via a virtual covalent bond to produce an interaction center chain, which is projected onto an underlying cubic lattice to produce a projected chain of interaction centers, and then secondary constraints and/or tertiary constraints are applied to a subset of, or all of, the interaction centers of the interaction center chain to generate a force field comprising short-range interactions, thereby producing a data set representing a three-dimensional model structure of the target protein.

In contrast, Oritz's method incorporates "predicted secondary and tertiary restraints into ab initio folding simulations" to generate "low resolution tertiary structures" of nonhomologous proteins. Oritz states "[s]econdary structural restraints are provided by the PHD secondary structure prediction algorithm that incorporates multiple sequence information. Predicted tertiary restraints are obtained from multiple sequence alignments via a two-step process: First, "seed" side chain contacts are identified from a correlated mutation analysis, and then, the seed contacts are "expanded" by an inverse folding algorithm. These predicted restraints are then incorporated into a lattice based, reduced protein model. Depending upon fold complexity, the resulting native-like topologies exhibit a coordinate root-mean-square deviation, cRMSD, from native between 3.1 and 6.7 A. Overall, this study suggests that the use of *restraints derived from multiple sequence alignments combined with a fold assembly algorithm* is a promising approach to the prediction of the global topology of small proteins. [emphasis added] (see abstract of Oritz). Oritz explores whether use of predicted secondary structure and tertiary restraints are adequate to predict tertiary structure *from sequence alone* [emphasis added] (see left-hand column, page 378, of Oritz).

Oritz does not produce an interaction center chain and project the interaction center chain onto an underlying cubic lattice to produce a projected chain of interaction centers by using a calculated force field comprising short-range interactions. Accordingly, because Oritz is not a

single prior source that contains each and every limitation of the claimed invention this rejection 35 U.S.C. 102(a) can be withdrawn.

Enclosed is a $475 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 2/12/04

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